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Prediction of high-flow nasal cannula failure in critically ill patients: a narrative review

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Abstract

High-flow nasal cannula (HFNC) therapy is widely used for respiratory support in critically ill patients, offering benefits such as improved oxygenation and reduced respiratory rate. However, HFNC failure can lead to adverse outcomes, including increased mortality. This narrative review examines predictive factors and indices for HFNC failure, including respiratory rate, P/F and S/F ratios, the ROX index, HACOR score, and emerging indices, such as VOX and FOX. Among these, the ROX index and HACOR score currently provide the most robust predictive value, whereas newer tools such as VOX and FOX require further validation. The ROX index, combining oxygenation and respiratory rate, has shown significant predictive value, particularly in COVID-19 patients, though its thresholds and timing for assessment remain variable. Modified versions of the ROX index, incorporating heart rate and PaO_2, have improved predictive accuracy. The HACOR score, initially developed for non-invasive ventilation, also predicts HFNC failure but may be less discriminative in emergency settings. Emerging indices such as VOX and FOX offer novel approaches but face clinical application challenges due to measurement complexities. Risk stratification models, scoring systems, ultrasound techniques, and machine learning methods show promise but require further validation. This review highlights the importance of integrating multiple predictive tools and tailoring assessments to individual patient conditions. Future strategies must also account for nursing quality variables to enhance prediction accuracy in real-world settings. Comprehensive training for healthcare professionals and future multicenter, large-scale studies is essential to refine these predictive strategies and improve patient care quality.

Keywords High-flow nasal cannula, Predictors of failure, ROX index, HACOR score

Background

High-flow nasal cannula (HFNC) is a respiratory support modality that delivers heated and humidified oxygen via the nasal route. HFNC can provide oxygen at a fraction of inspired oxygen (FiO_2) ranging from 0.21 to 1.0, with flow rates up to 60 l per minute or higher [1]. This technique maintains a stable oxygen concentration, reduces anatomical dead space, generates positive airway pressure, increases end-expiratory lung volume, elevates absolute transpulmonary pressure, decreases the work of breathing, and improves overall gas distribution in the lungs [2–5].

Since its introduction as a simple and well-tolerated form of respiratory support for critically ill patients, HFNC has gained widespread use in clinical practice, with its benefits partially validated. Compared to

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standard oxygen therapy, HFNC provides superior heating and humidification, which helps thin mucus, reduce its viscosity, and enhance patient comfort [6]. Studies conducted during the COVID-19 pandemic demonstrated that HFNC delivers higher oxygen concentrations, lowers intubation rates, and shortens ICU stays compared to conventional oxygen therapy for patients with respiratory failure [4, 5]. However, additional evidence is needed to establish clear criteria for HFNC success, failure, and therapy escalation. Currently, no unified standard exists for predicting HFNC outcomes and delayed or inappropriate withdrawal or escalation of HFNC can lead to adverse events. In particular, studies indicate that improper use of HFNC may result in poor outcomes, and late HFNC failure (occurring more than 48 h after initiation) is significantly associated with increased overall ICU mortality [6].

Early and accurate prediction of HFNC failure is critical for enabling timely clinical interventions and minimizing adverse events. This article aims to examine the factors influencing HFNC success or failure, identify key indicators of treatment failure, discuss the challenges in forecasting outcomes, and provide an overview of practical and comprehensive prediction strategies. Specifically, we emphasize that optimal prediction requires moving beyond static parameters to adopt dynamic, multi-time-point evaluations that integrate physiological trends with the patient's specific clinical profile.

Literature search strategy

This narrative review aimed to synthesize evidence on predictors of HFNC failure. Although a structured search strategy was used, study selection was narrative (non-systematic) and not intended to be exhaustive as in a formal systematic review. We searched PubMed/MEDLINE and Web of Science from inception to June 2025 using combinations of keywords including "high-flow nasal cannula", "HFNC", "predict*", "failure", and specific indices (e.g., "ROX index"). Screening was performed in two stages: (1) title/abstract screening, followed by (2) full-text assessment of potentially eligible studies. Study selection was conducted independently by two reviewers (S.-M.Z. and A.M.); disagreements were resolved by discussion and, when necessary, adjudicated by a third senior reviewer (M.Z.). We prioritized original studies and systematic reviews in adult critically ill patients and excluded pediatric studies, case reports, and editorials.

Definitions of HFNC failure

Definitions of HFNC failure in previous studies vary, but they generally fall into two main categories:

Upgrade to non-invasive ventilation (NIV) or alternate use. This occurs when a patient, during or after HFNC therapy, requires transition to or alternation with NIV [7–16].

Transition to invasive mechanical ventilation (IMV), ECMO, or death. This category includes patients who require IMV within a specified period (e.g., 7 days) after HFNC initiation, escalate to ECMO, or die within 28 days of starting HFNC therapy [11, 12, 15–33].

Risk factors for HFNC failure

HFNC failure in critically ill patients often results from the interplay of multiple factors. Clinical factors associated with HFNC failure are summarized in Table 1.

Patient baseline characteristics, disease severity, neurological status, laboratory results, and imaging findings all contribute to the risk. Age is a significant factor, with elderly patients exhibiting higher failure rates due to decreased physiological oxygen reserve and increased comorbidities, particularly those with higher Charlson Comorbidity Index scores [18, 21, 23, 28]. Indicators of disease severity, such as elevated SOFA, APACHE IV, and pneumonia severity index scores, reflect more severe organ dysfunction and acute illness, correlating with increased HFNC failure risk [12, 18, 25, 27, 28, 34]. Neurological status, assessed via lower GCS scores, may heighten failure risk due to impaired airway protection [11, 18]. Laboratory markers, including elevated pre-treatment BNP levels indicating cardiac insufficiency and higher CRP levels reflecting increased infection risk, are also linked to failure [12, 24, 25]. Furthermore, CT imaging findings of severe pneumonia, pulmonary edema, or other underlying pathologies increase the likelihood of HFNC failure [22, 25, 35]. Higher SAPS-II scores similarly indicate greater illness severity and an increased risk of failure [22, 34].

Predictors and indices for HFNC failure

Respiratory rate and breathing pattern

The safety and efficacy of HFNC therapy have been extensively investigated since 2010. In a comparative study of patients with acute respiratory failure (ARF), Roca et al. reported that HFNC improved clinical tolerance, enhanced oxygenation, and reduced respiratory rate [36]. Subsequent research in 2011 corroborated these findings, showing that HFNC significantly decreased respiratory rate, heart rate, and dyspnea scores while improving clinical indicators such as chest retractions, paradoxical breathing, and oxygen saturation [37]. A multicenter randomized controlled trial further demonstrated that, compared to standard oxygen therapy and NIV, HFNC reduced respiratory discomfort and improved dyspnea scores within the first hour of treatment [38]. Moreover, studies suggest that insufficient reduction in respiratory

Table 1 Risk factors for HFNC failure

Author	Sample characteristic	HFNC outcome (associated with failure/success)[a]	Risk factors
Zhao et al. [12]	HFNC after weaning from IMV ($n=99$)	HFNC failure: IMV/NIV	SOFA score, BNP before HFNC treatment and HR after HFNC treatment 30 min
Liu et al. [18]	COVID-19 ($n=652$)	IMV or death within 28 days after ICU admission	Age, number of comorbidities, ROX index, Glasgow Coma Scale Score, and use of vasopressors on the first day of NIRS
Garner et al. [27]	COVID-19 ($n=30$)	HFNC success: avoid intubation	Higher Sequential Organ Failure Assessment Score, and at least one comorbidity or history of immunosuppression
Goury et al. [28]	COVID-19 ($n=42$)	IMV	Success: younger, lower SOFA score, less fever, thrombopenia or leukopenia, and a higher ROX index at H12
Kansal et al. [20]	HFNC following extubation ($n=244$)	Re-intubation ≤7 days following extubation	Patients with stroke as a comorbidity, predicts poorer clinical outcomes
Lun et al. [11]	AHRF ($n=124$)	Escalation of treatment to NIV/IMV/ECMO/death	Higher Acute Physiology and Chronic Health Evaluation IV scores, lower Glasgow Coma Scale scores, lower platelet counts and serum sodium levels upon ICU admission, and higher pH on day of HFNC commencement, higher RR and higher HR, ROX index
Raboni et al. [21]	COVID-19 ($n=128$)	IMV	Charlson comorbidity score, need for oxygen flow and breathing frequency. ROX > 4.98 (in 6 h) and >4.53 (in 24 h) predicts HFNC therapy success, <3.47 predicts therapy failure
Ait Hamou et al. [22]	COVID-19 ($n=200$)	IMV	SAPS-2 score, extent of CT-scan abnormalities >75% and HFNC duration, ROX index
Fulya et al. [23]	COVID-19 ($n=70$)	IMV and mortality	Advanced age, male gender, and low ROX index
Schmidt et al. [24]	COVID-19 ($n=16$)	IMV	Elevated oxygen saturation, decreased FiO_2 and reduced serum CRP on day 4
Talpoș et al. [25]	COVID-19 ($n=52$)	IMV	Higher CRP values and more lung infiltrates on chest CT; at 24 h after admission: higher SOFA score, higher RR, higher FiO_2 requirement, and lower PaO_2, PaO_2/FiO_2 ratio, ROX index, and modified ROX index
Saillard et al. [34]	Cancer ($n=202$)	IMV	The absence of sepsis, $SpO_2 < 95\%$ 15 min after HFNC initiation, the number of pulmonary quadrants involved on chest X-ray, FiO_2 >60% at HFNC initiation, and SAPS II at ICU admission

AHRF acute hypoxemic respiratory failure, *NIV* non-invasive ventilation, *IMV* invasive mechanical ventilation, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *COVID-19* coronavirus disease 2019, *SOFA* Sequential Organ Failure Assessment, *RR* respiratory rate, *HR* heart rate, *HFNC* high-flow nasal cannula oxygen therapy, *CT* computed tomography, *CRP* C-reactive protein, *NIRS* non-invasive respiratory strategies, *BNP* brain natriuretic peptide, *SAPS-2* Simplified Acute Physiology Score-2, *LDH* lactate dehydrogenase, *NT-proBNP* N-terminal probrain natriuretic peptide

[a] Failure/success definition varies across studies

rate or increasing oxygen flow requirements during the first 6 h of HFNC therapy may predict treatment failure [39].

While HFNC effectively improves oxygenation, reduces respiratory rate, and alleviates dyspnea, early changes in these parameters may provide valuable insights into therapy outcomes. However, definitive cut-off values for predicting HFNC failure have not yet been established, highlighting the need for further studies to develop standardized predictive criteria.

P/F ratio and S/F ratio

The P/F ratio, defined as the arterial oxygen partial pressure (PaO_2) divided by the fraction of inspired oxygen (FiO_2), is widely used to assess oxygenation status. Clinically, it serves as a key indicator of respiratory function, particularly in conditions such as acute respiratory distress syndrome (ARDS). The Berlin Definition incorporates the P/F ratio into the grading criteria for ARDS severity [40]. Studies have demonstrated that, following 6 h of high-flow nasal cannula (HFNC) therapy, a

persistently low P/F ratio, increasing gas flow requirements, or hemodynamic instability may serve as predictive indicators of HFNC failure [39].

While the P/F ratio is crucial for assessing oxygenation status, its measurement requires arterial blood gas sampling, which can limit early diagnosis and timely intervention for ARDS, particularly in hospitals lacking necessary resources. In contrast, oxygen saturation (SpO_2) can be continuously monitored non-invasively and is widely available across clinical settings. Studies have demonstrated a positive correlation between the P/F ratio and the SpO_2/FiO_2 (S/F) ratio [41]. In a study involving 66 patients with a mean baseline S/F ratio of approximately 160 undergoing HFNC therapy, the S/F ratio showed superior predictive accuracy compared to the P/F ratio. The area under the receiver operating characteristic curve (AUROC) for the S/F ratio at 24 h post-HFNC initiation indicated excellent predictive performance, with an S/F ratio ≥170.9 identified as a reliable predictor of treatment success [42].

Although the PaO_2/FiO_2 ratio remains a valuable predictor, when arterial blood gas measurements are unavailable, the SpO_2/FiO_2 ratio is more suitable for early assessment and dynamic monitoring of HFNC outcomes. This approach is particularly advantageous in resource-limited settings. Nevertheless, further research is needed to validate the correlation between P/F and S/F ratios and to establish definitive clinical thresholds for widespread application.

ROX index and modified ROX index

The ROX index, introduced in 2016, is a predictive tool derived from respiratory variables, designed to distinguish between HFNC treatment success and failure. It is calculated as (SpO_2/FiO_2) divided by respiratory rate (RR, breaths/min). The numerator reflects variables positively associated with HFNC success, while the denominator represents those negatively associated, thereby providing an integrated predictor of HFNC outcomes [7]. Studies have demonstrated that the ROX index exhibits strong predictive value in patients with respiratory failure, both in COVID-19 and non-COVID-19 populations [15, 16, 43–48] (see Table 2). Research on the ROX index has primarily focused on identifying effective thresholds at different time points; however, evaluation times and cut-off values remain non-standardized, likely due to differences in patient populations and study endpoints [49–53]. According to the widely cited standard proposed by Roca et al., ROX indices below 2.85, 3.47, and 3.85 at 2, 6, and 12 h after HFNC initiation, respectively, are predictive of HFNC failure [17].

For specific populations such as post-extubation patients, those with COVID-19, or COPD, distinct ROX index thresholds have been identified. A multicenter study from Singapore demonstrated that, among ICU patients with pneumonia and those receiving sequential therapy post-extubation, a ROX index <6.06 at 1 h after HFNC initiation is a strong predictor of treatment failure [54]. For post-extubation patients, other studies reported that a ROX index >8.7 at both 2 and 6 h, and >10.4 at 12 h, indicates a higher likelihood of HFNC success [55]. The ROX index has also shown good predictive performance for HFNC failure in emergency AHRF patients [56]. When applied to adults with acute exacerbation of COPD receiving HFNC therapy, higher ROX index values are required to indicate a low risk of treatment failure. Specifically, a ROX score <4.88 is insufficient to accurately predict intubation or mortality in this population. The best predictive effect is only achieved when it is greater than 6.88 [57].

During the COVID-19 pandemic, research on HFNC use in COVID-19 patients expanded significantly [58, 59]. Among the studies reviewed regarding the ROX index, two-thirds of the patient cohort consisted of COVID-19 cases, reflecting a relatively advanced understanding of ROX index application in this population (see Table 3). A recent large-scale study ($n = 1847$) further identified that a ROX index <3.85 at 12 h post-HFNC initiation was highly specific (89.8%) for predicting the need for IMV [60].

A study evaluating the ROX index in patients with ARF demonstrated that it exhibits high sensitivity in COVID-19 patients with acute hypoxemic respiratory failure (AHRF), with lower ROX index values predicting a higher risk of mortality. Reviews of data in patients with community-acquired pneumonia (CAP) and COVID-19 indicated that an oxygenation index <99.6, a respiratory rate >27 breaths/min, and a ROX index <4.88 are predictive of HFNC failure. In addition, a CRB65 score >3 at admission and >2 at the initiation of HFNC therapy was associated with increased risk of treatment failure in COVID-19 patients [61].

According to studies included in a meta-analysis, the optimal ROX index cutoff for predicting HFNC failure within 24 h of admission is approximately 5 [62]. Lemiale et al. reported that the ROX index achieves its maximum diagnostic accuracy at 6 h after HFNC initiation [63]. Another meta-analysis suggested a general cut-off value of 5.23 for the ROX index, which maximizes both sensitivity and specificity regardless of timing [64]. Furthermore, the predictive performance of the ROX index improves when assessed beyond 6 h, with the summary area under the receiver operating characteristic curve (sAUC) increasing from 0.754 at 2–6 h to 0.795 at 6–12 h [64].

Table 2 Predictors of HFNC failure

Author	Sample characteristic	Predictor	Outcome	Cut-off	Sensitivity	Specificity
ROX in non-COVID-19 patient						
Roca et al. [7]	ARF ($n=157$)	ROX	IMV	4.88 at 12 h	N/A	N/A
Roca et al. [17]	Pneumonia ($n=191$)	ROX	Need or not for intubation	≥4.88 at 2 h ≥4.88 at 6 h ≥4.88 at 12 h <2.85 at 2 h <3.47 at 6 h <3.85 at 12 h	69.6% 83.8% 86.8%	60% 50% 52.2% 99.2% 99.2% 98.4%
Lemiale et al. [63]	Immunocompromised ($n=302$)	ROX	IMV	4.88 at 6 h	52.1%	68.9%
Lee et al. [55]	Post-extubation ($n=276$)	ROX	Reintubation within 72 h after extubation	8.7 at 2 h 8.7 at 6 h 10.4 at 12 h	55.2%	81.3%
Li et al. [43]	AHRF ($n=483$)	ROX	Intubation	6.06 at 1 h	51%	80%
Reyes et al. [44]	CAP ($n=895$)	ROX	IMV	14.8	77.8%	62.4%
Fuentes et al. [49]	Post-extubation ($n=162$)	ROX	inability to tolerate removal of IMV and the need for reintubation within 72 h after extubation because of hypoxemia ($PaO_2<60$ mmHg), non-permissible hypercapnia ($PaCO_2>60$ mmHg with pH < 7.2), or labored breathing	<4.88	N/A	N/A
Praphruetkit et al. [73]	AHRF ($n=75$)	ROX	HFNC success: no intolerance or escalation toward MV or NIV within 48 h	4.88 at 6 h	92.98%	61.11%
Kang et al. [56]	Emergency AHRF ($n=97$)	ROX ROX-HR	IMV	<5.614 <6.152	N/A	N/A
Schaeffer et al. [57]	AECOPD ($n=260$)	ROX	MV/death	>6.88	60%	62%
ROX of HFNC failure in COVID-19 patient						
Chandel et al. [47]	COVID-19 ($n=272$)	ROX	IMV	>3.0 at 2, 6, 12 h	85.3%	N/A
Duan et al. [70]	COVID-19 ($n=66$)	ROX	NIV/IMV	≤7.17 at 1 h	71%	70%
Suliman et al. [51]	COVID-19 ($n=69$)	ROX	IMV	≤25.26%[a]	90.2%	N/A
Ferrer et al. [52]	COVID-19 ($n=85$)	ROX	IMV/NIV/death	5.35 at 24 h	91%	79%
Valencia et al. [72]	COVID-19 ($n=245$)	ROX HACOR	IMV/death	5.6 5.5	62% 66%	65% 65%
Fulya et al. [23]	COVID-19 ($n=70$)	ROX	mortality and IMV	2.84	63.8%	69.6%
Sekar et al. [26]	COVID-19 ($n=127$)	ROX	IMV	2.97 at 2 h 3.63 at 6 h	87% 98%	82% 97%
Myers et al. [60]	COVID-19 ($n=1847$)	ROX	IMV or death	3.85 at 12 h	32.3%	89.8%
Vega et al. [31]	COVID-19 ($n=35$)	ROX	IMV/death	5.99 at 12 h	64%	96%
Kim et al. [29]	COVID-19 ($n=133$)	ROX S/F	IMV	8.54 at 1 h 166 at 1 h	59.6% 79.3%	26.1% 37.3%

Table 2 (continued)

Author	Sample characteristic	Predictor	Outcome	Cut-off	Sensitivity	Specificity
Küçük et al. [35]	COVID-19 ($n=85$)	ROX CT score	IMV/death	<3.81 >15	78.26% 65.3%	58.97% 44.44%
Vest et al. [32]	COVID-19 ($n=1087$)	ROX	mortality	≥4.88 at the time of intubation	N/A	N/A
Weerasuriya et al. [30]	COVID-19 ($n=146$)	ROX	escalation to CPAP/IMV/death due to respiratory failure prior to CPAP or IMV	N/A	N/A	N/A
Bhuiyan et al. [13]	COVID-19 ($n=44$)	ROX	discontinue or deescalate respiratory support as a part of continuous positive airway pressure (CPAP) ventilation success	HFNC success: 3.9 CPAP success: 2.64	90.3% 85.7%	76.9% 83.3%
Romero et al. [46]	COVID-19 ($n=97$)	ROX	IMV	6.23 at 12 h	0.85	0.55
Poopipatpab et al. [58]	COVID-19 ($n=212$)	ROX	ROX index ≤4.88	5.84	80.2%	86.9%
Abroug et al. [53]	COVID-19 ($n=213$)	ROX	A ΔROX cutoff ≤1.8 had the best combination of characteristics in predicting the failure of HFNC	ΔROX ≤ 1.8	0.89	0.61
Basoulis et al. [16]	COVID-19 ($n=1115$)	ROX	HFNC success: improved oxygenation, no need for NIV and/or IMV	4.43 at 12 h	64.5%	69.65
Hancı et al. [15]	COVID-19 ($n=69$)	ROX	NIV/IMV	5.5 at 12 h	N/A	N/A
Ruangsomboon et al. [48]	COVID-19 ($n=173$)	S/F ROX mROX	HFNC success: no requirement of IMV at HFNC termination	128.19 at 2 h 3.23 4.27	65.3% 97.5% 78.8%	61.8% 23.6% 38.2%
Okazaki et al. [59]	COVID-19 ($n=248$)	ROX	reintubation	7.44 at 0 h	0.42	0.97
Grünewaldt et al. [61]	COVID-19 & CAP ($n=245$)	ROX RR Oxygenation index	IMV or death	<4.88 >27 <99.6	75% 74%	59% 81%
Other predictors of HFNC failure						
Koyauchi et al. [42]	AE-ILD ($n=66$)	S/F	HFNC success: HFNC withdrawal with improved oxygenation, and other outcomes were defined as HFNC failure	170.9 at 24 h	96.2%	68.4%
Goh et al. [65]	Post-extubation ($n=145$)	ROX-HR	IMV	8.0 at 10 h	84.6%	63.6%
Xu et al. [79]	COVID-19 ($n=324$)	A risk stratification	IMV	6	80.3%	71.2%
Magdy and Metwally [71]	AHRF ($n=150$)	HACOR	IMV/death	6 after 1 h	81.2%	91%
Li et al. [75]	ARF ($n=46$)	EIT	Reintubation within 48 h after HFNC	Not relevant	N/A	N/A
Varipapa et al. Jr [33]	RF ($n=74$)	Fluid balance and ROX	HFNC outcomes: success (wean from HFNC) and failure (require IMV)	Negative fluid balance	N/A	N/A
Karim et al. [67]	COVID-19 ($n=27$)	mROX	NIV or IMV	4.05 at 6 h	87.5%	63.16%

Table 2 (continued)

Author	Sample characteristic	Predictor	Outcome	Cut-off	Sensitivity	Specificity
Li et al. [66]	AHRF ($n=75$)	mROX	improvement of respiratory status without requiring intubation for MV	4.3 at 2 h	96.1%	70.8%
Chen et al. [74]	AHRF (N = 62)	VOX	IMV	22.67	86.21%	90.91%
Parke et al. [76]	Type I and II RF ($n=70$)	FOX	NIV/IMV/admission to an ICU/death	>19 at 6 h <14.1	N/A	N/A
Kansal et al. [69]	ARF ($n=111$)	ΔPOX-HR POX-HR	escalate to intubation or NIV within 48 h of HFNC application for respiratory causes only	>0.1 >6.8	79.2% 77.8%	71.8% 64.1
Saillard et al. [34]	Cancer ($n=202$)	Duration of HFNC	IMV	N/A	N/A	N/A
Ai et al. [68]	COVID-19 ($n=60$)	mROX	IMV	4.45 at 2 h	92%	94%
Talpoș et al. [25]	COVID-19 ($n=52$)	mROX ROX PaO_2/FiO_2	IMV	4.94 at 24 h 5.63 at 24 h 123.6 at 24 h	81% 68% 87%	90% 95% 81%
Bruna et al. [85]	COVID-19 ($n=41$)	Diaphragmatic contraction speed	IMV/death	1.35 cm/segment	89%	57%
Yang et al. [86]	–	Machine learning by EIT features	HFNC outcomes	XGboost	N/A	80%
Aguirre-García et al. [80]	COVID-19 ($n=529$)	Risk stratification	IMV/death	N/A	N/A	N/A
Okano et al. [84]	COVID-19 ($n=300$)	HACOR ROX	Intubation or death within 7 days	>5 <2.85	18% 3.9%	91% 100%
Koyama et al. [87]	COVID-19 ($n=122$)	LDH IL-6	transfer to intensive care just before/after intubation or in-hospital death	a lesser reduction	N/A	N/A
Yu et al. [81]	COVID-19 ($n=184$)	SVM	The success and failure of big data analysis	N/A	73%	73%
Cheng et al. [82]	AHRF ($n=522$)	ML	Models based on ensemble learning outperformed other models	N/A	N/A	N/A
Li et al. [83]	AHRF ($n=427$)	LSTM	It performed better than traditional indicators in internal verification	N/A	N/A	N/A
Ikeda et al. [88]	COVID-19 ($n=194$)	CRP and D-dimer	The median CRP ratio of intubated patients was relatively low	N/A	N/A	N/A
Xue et al. [89]	AHRF ($n=388$)	CT score, SOFA score, IL-1β and albumin	CT score, SOFA score, IL-1β, and albumin are independent predictors of HFNC failure	N/A	N/A	N/A

AHRF acute hypoxemic respiratory failure, *ARF* acute respiratory failure, *RF* respiratory failure, *RR* respiratory rate, *NIV* non-invasive ventilation, *IMV* invasive mechanical ventilation, *MV* mechanical ventilation, *FiO_2* fraction of inspired oxygen, *SpO_2* peripheral oxygen saturation by pulse oximetry, *EIT* electrical Impedance tomography, *CPAP* continuous positive airway pressure, *CAP* community-acquired pneumonia, *S/F* SpO_2/FiO_2, *AE-ILD* acute exacerbation of interstitial lung diseases, *ICU* intensive care unit, *HFNC* high-flow nasal cannula oxygen therapy, *HFOT* high-flow oxygen therapy, *COVID-19* coronavirus disease 2019, *CT* computed tomography, *SVM* support vector machine, *LDH* lactate dehydrogenase, *IL-6* interleukin-6, *ML* machine learning, *LSTM* long short-term memory, *CRP* C-reactive protein, *IL-1β* interleukin-1β, *SOFA* Sequential Organ Failure Assessment

[a] This study reported ROX using a non-standard scaling/format; values should not be directly compared with studies using the conventional ROX calculation

Table 3 Formulas for predictor scores

Predictors score	Formula		
ROX	$(SpO_2/FiO_2)/RR$		
ROX-HR	(ROX/HR) × 100		
mROX	$(PaO_2/FiO_2)/RR$		
mROX-HR = POX-HR	$[(PaO_2/FiO_2)/RR]/HR \times 100$		
VOX	$(SpO_2/FiO_2)/VT$		
MOX	$(SpO_2/FiO_2)/MV$		
FOX	(Flow * FiO_2)/SpO_2		
HACOR	Heart rate	<120	0
		≥121	1
	Acidosis (PH)	≥7.35	0
		7.30–7.34	2
		7.25–7.29	3
		<7.25	4
	Consciousness (GCS)	15	0
		13–14	2
		11–12	5
		≤10	10
	Oxygenation (PaO_2/FiO_2)	≥201	0
		176–200	2
		151–175	3
		126–150	4
		101–125	5
		≤100	6
	Respiratory rate	≤30	0
		31–35	1
		36–40	2
		41–45	3
		≥46	4

In recent years, the ROX index has undergone several modifications to enhance its predictive accuracy for HFNC treatment failure (see Table 3). In 2020, the ROX-HR index (Respiratory Oxygenation-Heart Rate Index) was introduced, combining the ROX index with heart rate (HR) to improve prediction. Studies demonstrated that low ROX and ROX-HR values within 1–48 h were associated with HFNC failure, whereas a ROX-HR >6.80 at 10 h indicated a significantly lower risk of failure. For patients receiving sequential HFNC therapy post-extubation, ROX-HR values between 1 and 24 h strongly correlated with outcomes, with a ROX-HR >8.00 at 10 h predicting treatment success [65].

To enhance predictive accuracy, the modified ROX index ($mROX = PaO_2/FiO_2/RR$) was introduced, incorporating arterial oxygen partial pressure into the calculation. Comparative studies demonstrated that mROX and mROX-HR indices outperformed traditional ROX and ROX-HR in predicting HFNC success at 2 h. Specifically, an mROX >4.30 showed the highest sensitivity (96.1%) at 2 h, while a baseline mROX >7.10 achieved maximum specificity (100%) for successful outcomes [66].

In 2022, a study reported that both baseline and 6-h ROX and mROX indices demonstrated strong predictive accuracy and favorable AUC values in COVID-19 patients. Specifically, an mROX <4.05 at 6 h post-HFNC was identified as a valuable screening tool for early risk stratification [67]. Furthermore, a multicenter study involving 60 COVID-19 patients showed that an mROX <4.45 at 2 h reliably predicted the need for IMV, suggesting that early identification and timely intubation could improve survival outcomes [68].

In another study, the ROX index was further modified by replacing the SpO_2/FiO_2 ratio with the PaO_2/FiO_2 ratio and incorporating heart rate, resulting in the POX-HR index. The Delta POX-HR, defined as the change in POX-HR before and after HFNC initiation, demonstrated the highest predictive accuracy. Specifically, a Delta POX-HR >0.1 was significantly associated with a lower risk of HFNC failure, suggesting that this dynamic metric may enhance the reliability of outcome prediction for HFNC therapy [69].

These modified ROX indices provide improved precision over the traditional ROX index, enabling earlier identification of high-risk patients and supporting optimized treatment strategies. Relevant formulas and supporting studies are summarized in Tables 2 and 3.

In summary, the ROX index is a valuable tool for assessing the effectiveness of HFNC therapy; however, its threshold values and optimal assessment timing remain incompletely standardized. Modified ROX indices that incorporate additional parameters, such as heart rate and PaO_2, have markedly improved predictive accuracy. These enhanced indices are particularly useful in specific patient populations, including COVID-19 patients and those receiving sequential post-extubation HFNC therapy. The development of these refined tools supports personalized management and timely intervention, providing clinicians with more precise guidance for optimizing HFNC treatment outcomes. Note that ROX values depend on how SpO_2 is expressed (percentage vs. fraction); therefore, cutoffs should be interpreted using the same calculation approach as in the original validation study.

HACOR score

Similar to the ROX index, the predictive utility of the HACOR score can vary by clinical setting. The HACOR score was originally developed to predict NIV failure in patients with type I respiratory failure. It comprises five

indicators: heart rate (beats/min), acidosis (pH), consciousness level (assessed via the Glasgow Coma Scale), oxygenation status (PaO_2/FiO_2), and respiratory rate (breaths/min) [70]. The score has since been adapted to predict outcomes of HFNC therapy, with relevant formulas and supporting studies summarized in Tables 2 and 3. Research indicates that the HACOR score reliably predicts HFNC failure within 1 h of initiation, with a score >6 achieving an accuracy of 85% [71].

A study involving 245 COVID-19 patients compared the predictive accuracy of the HACOR score and the ROX index for HFNC failure. Both scales demonstrated similar AUROC values (ROX 0.72 vs. HACOR 0.71), with optimal cut-off points estimated using the Liu method at 5.6 for ROX and 5.5 for HACOR. The study suggested that combining these scores with additional clinical variables could improve predictive performance [72].

However, in emergency patients with respiratory failure, the ROX index exhibited superior discriminatory ability. Measured at 6 h, a ROX threshold of 4.88 predicted HFNC success with a sensitivity of 92.98%, specificity of 61.11%, positive predictive value of 88.33%, negative predictive value of 73.33%, and overall diagnostic accuracy of 85.33% [73].

Both the HACOR score and ROX index have unique characteristics and clinical applications. While their predictive performance can be comparable in some populations, relying on a single metric may be insufficient. In practice, integrating ROX and HACOR alongside other clinical variables may provide a more comprehensive and individualized assessment than relying on a single metric.

VOX index and FOX index

Recently, a novel predictive indicator, the VOX index, has been introduced. The VOX index incorporates respiratory drive by measuring the patient's exhaled tidal volume (VT) during HFNC treatment via a NIV test and combines this with the S/F ratio. This approach provides an early, dynamic assessment of HFNC efficacy. Studies have shown that the VOX index offers greater predictive value than the ROX index while requiring less observation time. At 6 h post-HFNC initiation, the VOX index demonstrated a sensitivity of 86.21% and a specificity of 90.91% [74].

Another research group observed discrepancies between VT measurements obtained via electrical impedance tomography (EIT) and those from NIV experiments. To address this, they proposed replacing VT with minute ventilation (MV) measured by EIT, leading to the development of a new predictive metric, the MOX index. This index improves the accuracy of HFNC failure prediction while eliminating the need for direct VT measurement [75].

In addition to FiO_2, HFNC settings include temperature and flow rate. Physiologically, the flow rate is closely linked to the generation of a positive end-expiratory pressure (PEEP) effect, which plays a crucial role in patient oxygenation [76, 77]. Accordingly, some researchers incorporated flow rate into predictive formulas, leading to the development of the FOX index. A FOX index ≥19 within 6–24 h was associated with HFNC treatment failure [78]. The VOX and FOX formulas, along with their corresponding studies, are summarized in Tables 2 and 3.

Although the VOX index demonstrates superior predictive efficiency compared to the ROX index, its clinical use is limited by the difficulty of measuring VT, which requires advanced equipment and technical expertise, increasing operational complexity and costs. The MOX index addresses this limitation by replacing VT with MV measured via EIT, simplifying the workflow. However, it introduces new constraints, including reliance on EIT technology, the need for specialized equipment and trained personnel, and applicability limited to selected patient populations. The FOX index offers a unique perspective by incorporating HFNC flow rate into its predictive formula, but it does not fully account for other factors affecting oxygenation, such as mouth versus nasal breathing, potentially limiting its predictive robustness. Collectively, these indices each have distinct strengths and weaknesses, underscoring the need for further refinement and context-specific application in clinical practice.

Machine learning and other predictive methods

In recent years, the construction of smart ICU information databases has advanced research on predicting HFNC treatment failure, with risk models and machine learning methods being widely applied. A 2020 retrospective analysis of 324 patients in Wuhan identified high-risk factors such as advanced age and low ROX index [79]. In 2023, Bruna M's team conducted an analysis of 529 patients, establishing clinical risk factors and developing a scoring system [80].

Since 2024, scholars have used machine learning to optimize predictive indicators. It was found that the accuracy of arterial blood gas (ABG) analysis was higher than that of the ROX index and mROX index, and the validation of the Support Vector Machine (SVM) model yielded favorable predictive results [81]. Subsequent models further identified predictive factors including the GCS score and SOFA score [82].

Recent studies have incorporated long short-term memory (LSTM) networks to optimize models, achieving higher accuracy than the ROX and mROX index [83]. In addition, a machine learning model integrated with a dynamic real-time early warning system indicated that

the predictive performance of the HACOR score and ROX index within 2 h may be insufficient [84].

Regarding new predictive approaches, the diaphragmatic contraction velocity measured via ultrasound technology requires further validation [85]. The XGboost model, when combined with electrical impedance tomography (EIT) image features, shows potential for early prediction but has certain limitations [86]. Among laboratory indicators, lactate dehydrogenase (LDH) and IL-6 levels within 1–3 days, viremia on days 4 or 7, as well as CRP levels, CT scores, and interleukin-1β (IL-1β) levels, have all been identified as independent predictors of HFNC treatment failure [87–89].

However, existing methods rely on specific indicators and high-quality databases, which limits their application in resource-constrained settings. Ultrasound technology also faces challenges in standardization that need to be addressed. Despite these limitations, these advancements collectively provide new directions for HFNC evaluation and clinical practice.

Conclusion and future prospects

HFNC therapy has become an effective respiratory support method, and predictive tools for treatment failure have advanced considerably. Current evidence highlights that the ROX index and HACOR score serve as the most validated key indicators, whereas others—such as respiratory rate, P/F and S/F ratios, and emerging indices such as VOX and FOX—provide supplementary value. The predictive performance and optimal thresholds for HFNC failure are highly dependent on the specific clinical population. However, clinicians must be aware that a "one-size-fits-all" threshold does not exist. For example, in COVID-19 cohorts, a ROX index <3.85 at 12 h has been repeatedly reported as a high-risk threshold, whereas in post-extubation sequential HFNC, higher ROX-derived thresholds are typically associated with success (e.g., >8.7 at 6 h).

Given the significant variation in predictive indicators and cut-off values for HFNC failure across different clinical contexts, and to avoid overgeneralization while enhancing clinical utility, Table 4 summarizes the key predictive tools, critical thresholds, and assessment notes for the major patient populations discussed.

Furthermore, there is no single tool that can reliably predict HFNC failure in isolation. In clinical practice, it is necessary to integrate multiple indicators through a stratified approach—potentially using the ROX index for serial screening and trend monitoring and using the HACOR score as a complementary confirmation tool in selected patients/scenarios (e.g., when hypercapnia/acid–base or neurologic status is clinically relevant). Meanwhile, the escalation decisions should incorporate the overall clinical trajectory rather than a single cut-off value. In the future, multicenter, large-scale studies should be conducted to incorporate nursing quality variables (such as humidification efficiency and patient comfort), optimize predictive parameters, and enable earlier,

Table 4 Key predictive indices across clinical scenarios

Population	Primary predictive tool(s)	Key cut-off/timepoint	Clinical notes
AHRF/pneumonia	ROX index	2 h < 2.85 6 h < 3.47 12 h < 3.85	Widely cited benchmark for non-COVID-19 pneumonia with hypoxemia
COVID-19 patients	ROX index	12 h < 3.85 (highly specific)	Most validated threshold for this population. ROX index shows high sensitivity
	HACOR score	≈5.5	Predictive performance comparable to ROX index (AUROC ~ 0.71)
Post-extubation patients	ROX index	1 h < 6.06 (predicts failure); 2/6 h > 8.7 and 12 h > 10.4 (predicts success)	Higher thresholds are generally required to predict success in sequential therapy
	ROX-HR index	10 h > 8.00 (predicts success)	Incorporates heart rate; strongly correlates with outcomes in this group
COPD patients (acute exacerbation)	ROX index	>6.88 (indicates low failure risk)	This population requires a much higher ROX index to indicate a low risk of intubation
Emergency department	ROX index	6 h < 4.88	Demonstrates superior discriminatory ability compared to HACOR score in this setting
	HACOR score	1 h > 6 (predicts failure)	Reliable predictor in general AHRF but may be less discriminative in emergency settings

HFNC high-flow nasal cannula oxygen therapy, *AHRF* acute hypoxemic respiratory failure, *COVID-19* coronavirus disease 2019, *COPD* chronic obstructive pulmonary disease

more accurate detection of treatment failure to improve patient outcomes.

Abbreviations

HFNC	High-flow nasal cannula oxygen therapy
NIV	Non-invasive ventilation
IMV	Invasive mechanical ventilation
MV	Mechanical ventilation
PaO_2	Partial pressure of oxygen
$PaCO_2$	Partial pressure of carbon dioxide
AE-ILD	Acute exacerbation of interstitial lung diseases
KNN	K-nearest neighbor
XGBoost	EXtreme gradient boosting
GBDT	Gradient boosting decision tree
AdaBoost	Adaptive boosting
CT	Computed tomography
COVID-19	Coronavirus disease 2019
RF	Respiratory failure
ARF	Acute respiratory failure
AHRF	Acute hypoxemic respiratory failure
ICU	Intensive care unit
P/F	PaO_2/FiO_2
S/F	SpO_2/FiO_2
FiO_2	Fraction of inspired oxygen
SpO_2	Peripheral oxygen saturation (pulse oximetry)
RR	Respiratory rate
BNP	Brain natriuretic peptide
APACHE II	Acute Physiology and Chronic Health Evaluation II
SOFA	Sequential Organ Failure Assessment
GCS	Glasgow Coma Scale score
CRP	C-reactive protein
SAPS-II	Simplified Acute Physiology Score-II
ARDS	Acute respiratory distress syndrome
EIT	Electrical impedance tomography
VT	Tidal volume
HR	Heart rate
PEEP	Positive end-expiratory pressure
CPAP	Continuous positive airway pressure
IL-6	Interleukin-6
AUROC	Area under the receiver operating characteristic curve
ECMO	Extracorporeal membrane oxygenation
NIRS	Non-invasive respiratory strategies
CAP	Community-acquired pneumonia
PH	Potential of hydrogen
IL-Iβ	Interleukin-1β
LDH	Lactate dehydrogenase
LSTM	Long short-term memory
SVM	Support vector machine
ML	Machine learning
COPD	Chronic obstructive pulmonary disease

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ZM, LK and YM conceived the study, designed the trial, and supervised the conduct of the trial. AM, ZSM completed the data collection and managed the data. LK and YX drafted the article. ZM and LK take responsibility for the paper.

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Declarations

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